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JUN 13 2014

510(K) SUMMARY

This 510(k) Summary is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K132978

A. Submitter

Sequenom, Inc.
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Date Prepared: June 12, 2014

B. Device Names and Regulatory Information

ASSAY

Common or Usual Name:	Factor V Leiden and Factor II genotyping test
Proprietary Name	IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test
Classification Name	Factor V Leiden DNA mutation detection systems (21 CFR 864.7280)
Classification	Class II
Product Code	PHJ: System, mass spectrometry, multiplex genotyping, hereditary thrombophilia related mutations
Panel	Hematology (81)

C. Predicate Devices

ASSAY
Roche Factor V Leiden Kit (K033607)
Roche Factor II (Prothrombin) G20210A Kit (K033612)

INSTRUMENT
Roche LightCycler® (K033734)
AutoGenomics INFINITI™ System (K060564)

D. Device Description

IMPACT Dx Factor V Leiden and Factor II Genotyping Test Overview

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is a qualitative, multiplexed genetic testing device for parallel detection and genotyping of the point mutations G1691A of the Factor V gene and G20210A of the Factor II gene from genomic DNA isolated from EDTA anti- coagulated human whole blood samples. The test is to be performed on the IMPACT Dx System.

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is performed using the IMPACT Dx System, which includes the IMPACT Dx NANO and the IMPACT Dx MA, a matrix-assisted laser desorption / ionization time-of-flight (MALDI-TOF) mass spectrometer. The test involves Factor V and Factor II region-specific polymerase chain reaction (PCR) amplification of genomic DNA purified from human whole blood in a multiplexed reaction, followed by allele-specific single base primer extension reactions. The reaction products are desalted, dispensed onto a SpectroCHIP® Array using the IMPACT Dx NANO, and the genotyping products are resolved on the basis of mass using the IMPACT Dx MA.

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test provides reagents for multiplex PCR, deoxynucleotide triphosphate dephosphorylation, and single base extension. The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is comprised of the following components:

- IMPACT Dx Factor V Leiden and Factor II Primer Set
- IMPACT Dx PCR Reagent Set
- IMPACT Dx Extend Reagent Set

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test utilizes a biochemistry process (Sequenom Biochemistry) that involves target-specific PCR amplification and single-base extension reactions with the subsequent analysis of the reaction products of the target nucleic acids by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

IMPACT Dx System Overview

The IMPACT Dx System (System) is a platform for highly accurate and sensitive genomic analysis and is designed for use with FDA cleared or approved assays citing its use. The IMPACT Dx System is comprised of the following instruments, software and consumables:

- IMPACT Dx NANO (NANO)
- IMPACT Dx MA (MA)
- TYPER Dx Software (TYPER Dx)
- System Consumables
  - SpectroCHIP® Arrays (Chip)
  - Clean Resin
  - 3-Point Calibrant (Calibrant)

The System is intended to be used by trained operators in a professional laboratory to perform the following key tasks:

- De-salt (using Clean Resin) amplified nucleic acid samples, upon completion of polymerase chain reaction (PCR) and single-base extension reactions following the instructions provided in the Sequenom test-specific package insert;
- Transfer (using the IMPACT Dx NANO) de-salted nucleic acid samples from a microtiter plate onto a disposable 96-pad sample Chip;
- Obtain mass spectra (using the IMPACT Dx MA) from samples and 3-Point Calibrant on a Chip; and
- Analyze (using the TYPER Dx software) the mass spectra of the samples for genotyping results.

The IMPACT Dx System accomplishes genomic analysis and genotyping testing by coupling a biochemistry process (Sequenom biochemistry) that involves target-specific PCR amplification and single-base extension reactions with the subsequent analysis of the reaction products of the target nucleic acids by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). This biochemistry process is homogeneous and does not require purification of the PCR products or the extension products and thus is very amenable to high-throughput genotyping testing.

IMPACT Dx NANO

The IMPACT Dx NANO is a self-contained, enclosed instrument that uses computer-controlled robotics to transfer nanoliter volumes of analyte from a 96-well microtiter plate onto a Chip, which is subsequently processed by means of MALDI-TOF MS analysis on the IMPACT Dx MA. This instrument includes an integrated computer pre-loaded with the Nanodispenser software and provides a simple touch-screen interface for users.

IMPACT Dx MA

The IMPACT Dx MA is a bench top mass spectrometer that processes analyte-loaded Chips by means of MALDI-TOF MS analysis. This instrument includes an integrated computer pre-loaded with the TYPER Dx software, a monitor, and a firewall for secure communication with the IMPACT Dx NANO. The main function of the IMPACT Dx MA is to acquire mass spectra from analytes that have been transferred onto a Chip, which has a chemical matrix on each pad. The mass spectra are captured and further analyzed by the TYPER Dx software.

TYPER Dx Software

The TYPER Dx software (TYPER Dx) manages the processing of Sequenom genotyping tests. It is deployed on the computer embedded within the IMPACT Dx MA.

The TYPER Dx software provides the following key functions:

- Allows users to create and manage panel runs;
- Monitors analyte transfer activities on the IMPACT Dx NANO;
- Controls user-initiated, automated mass spectrum acquisition runs on the IMPACT Dx MA;
- Analyzes the mass spectra acquired by the IMPACT Dx MA and makes genotype calls per a test-specific algorithm;
- Enables users to view and export results; and
- Allows an administrator to manage users to ensure secure access to the IMPACT Dx MA and panel run data.

E. Intended Use

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is a qualitative *in vitro* diagnostic device intended for use in the detection and genotyping of a single point mutation (G1691A, referred to as the Factor V Leiden mutation or FVL) of the Factor V gene, located on Chromosome 1q23, and a single point mutation (G20210A) of the prothrombin gene (referred to as Factor II or FII), located on Chromosome 11p11-q12, from genomic DNA isolated from EDTA anti-coagulated human whole blood samples. The test is to be performed on the IMPACT Dx System and is indicated for use as an aid in the diagnosis of patients with suspected thrombophilia.

F. Comparison with Predicate Devices

ASSAY

The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is substantially equivalent to the legally marketed predicate devices. These devices have the same intended use and indications for use and similar technological characteristics and principles of operation. They are all PCR-based tests for the genotyping of the Factor V and Factor II genes, with essentially the same performance characteristics. They use different signal detection methodologies and run on different instrumentation platforms; however, all are based on similar technological principles. Table F.1 below presents the similarities and differences between the assay and the predicate devices.

Table F.1
Substantial Equivalence – Comparison to Predicate Devices

	Device	Predicate	
	IMPACT Dx Factor V Leiden and Factor II Genotyping Test	**Roche Factor V Leiden Kit**	**Roche Factor II (Prothrombin) G20210A Kit**
510(k) Number	K132978	K033607	K033612
Type of Test	Genotyping Test	Genotyping Test	Genotyping Test
Measurand	Factor II and Factor V	Factor V	Factor II
Target of Detection	Single-nucleotide polymorphism	Single-nucleotide polymorphism	Single-nucleotide polymorphism
Intended User	Health Care Professional	Health Care Professional	Health Care Professional
Intended Use	Qualitative *in vitro* diagnostic genotyping test for the detection of Factor II and Factor V alleles from EDTA anti-coagulated human whole blood samples	Qualitative *in vitro* diagnostic genotyping test for the detection Factor V only in EDTA anti-coagulated whole blood samples	Qualitative *in vitro* diagnostic genotyping test for the detection of Factor II only in EDTA anti-coagulated whole blood samples
Indications for Use	Aid in the diagnosis of patients with suspected thrombophilia	Aid in the diagnosis of patients with suspected thrombophilia	Aid in the diagnosis of patients with suspected thrombophilia
Specimen Type	Purified DNA from human blood samples	Purified DNA from human blood samples	Purified DNA from human blood samples
Technological Detection Principles	Genotyping test for simultaneous detection (multiplex system) of PCR-amplified DNA sequences	Genotyping test for PCR-amplified DNA sequences	Genotyping test for PCR-amplified DNA sequences
Sample Preparation	DNA extraction and purification performed off-line	DNA extraction and purification performed off-line	DNA extraction and purification performed off-line
Oligonucleotide probes and primers	Specific for Factor V Leiden (G1691A) and Factor II G20210A	Specific for Factor V Leiden (G1691A)	Specific for Factor II (prothrombin G20210A)
Detection Chemistry	SNP discrimination by allele-specific single nucleotide extension coupled with MALDI-TOF mass spectrometry	Fluorogenic detection of PCR-amplification products by melting curve analysis	Fluorogenic detection of PCR-amplification products by melting curve analysis
Analytical Sensitivity	200 allele copies (0.67 ng input DNA/reaction)	FV: 50 allele copies / reaction	FII: 50 allele copies / reaction
Instrument	IMPACT Dx System	Roche LightCycler	Roche LightCycler
Controls	Internal control per sample plus external positive and negative controls required per run	External positive and negative controls required per run	External positive and negative controls required per run
Reference Method	Bi-directional DNA sequencing	DNA sequencing	DNA sequencing

INSTRUMENT

The IMPACT Dx System is substantially equivalent to the currently legally marketed predicate devices. These devices have the same intended use and similar technological characteristics and principles of operation. They are PCR-based genotyping instruments using detection of single nucleotide polymorphisms and have essentially the same performance characteristics. Table F.2 below presents the similarities and differences between the IMPACT Dx System and predicate devices.

Table F.2
Substantial Equivalence -- Comparison with Predicate Device

	Device	**Predicate**	
	Sequenom IMPACT Dx™ System	Roche LightCycler®	AutoGenomics INFINITI™ System
510(k) Number	K132978	K033734	K060564
Intended Use	Simultaneous, qualitative detection of multiple analytes in a PCR amplified genomic DNA sample utilizing MALDI-TOF MS.	A fully automated amplification and detection system for nucleic acids using fluorescence detection.	Designed to measure fluorescence signals of labeled DNA target hybridized to BioFilmChip microarrays
Intended User	Clinical laboratory	Clinical laboratory	Clinical laboratory
Specimen Type	Purified nucleic acids	Purified nucleic acids	Purified nucleic acids
Specimen Preparation	Performed off-line	Performed off-line	Performed off-line
Test Principle	MALDI-TOF detection (multiplex system) of PCR-amplified DNA sequences	Fluorogenic detection of PCR-amplified DNA fragments by melting curve analysis	Fluorogenic detection (multiplex system) of PCR-amplified DNA fragments
Detection Procedure	Mass spectrometric analysis of target-specific sequences.	Optical detection of stimulated fluorescence	Optical detection of simulated fluorescence
Detection Chemistry	Single-base extension reactions with the subsequent analysis using MALDI-TOF MS	Paired hybridization probes using fluorescence resonance energy transfer	Direct fluorescence

G. Non-clinical Bench Data

A series of internal and external analytical studies were conducted which demonstrated that the IMPACT Dx Factor V Leiden and Factor II Genotyping Test has equivalent performance compared to the predicate devices with respect to analytical sensitivity, analytical specificity, reproducibility and potential interfering substances and mutations. In addition, studies were conducted to verify that sample-to-sample contamination did not occur during the test procedure when used with the IMPACT Dx System. Lastly, in a study using fresh EDTA anti-coagulated whole blood samples collected from normal human subjects, DNA was extracted using the recommended DNA extraction method. The IMPACT Dx Factor V Leiden and Factor II Genotyping Test demonstrated 100% concordance with the reference bi-directional sequencing method on genotypes of both Factor II and Factor V genes.

Analytical Specificity

To determine the specificity of the extension primers, the extension primers were evaluated individually in the extension reactions using 13 clinical genomic DNA from patient samples encompassing all relevant genotypes for Factor VL and Factor II. All clinical samples produced the expected genotype calls, in respect to the extension primer under evaluation. When all extension primers in the IMPACT Dx Factor V Leiden and Factor II Genotyping Test were evaluated together, similarly, all clinical samples produced the expected genotype calls for both FII and FVL.

Interfering Mutations

In studies to evaluate the effect of mutations in close proximity to genotyping at locus 1691 of the FVL gene, as well as locus 20210 on the FII gene, the variants were tested in each of the 4 reactions. No FVL or FII genotype will be reported on the patient specimens when the Factor V forward assay fails to produce a genotype call due to the presence of an interfering 1690 C>T or 1692A>C or on a patient specimen when the Factor II forward assay fails to produce a genotype call due to the presence of either the 20207A>C or 20209C>T interfering mutations. No miscall or unexpected call from any of the samples was observed during the evaluation.

Analytical Sensitivity

Clinical genomic DNA obtained from patient samples encompassing all relevant genotypes for Factor V and Factor II genes were used to determine the limits of detection of the IMPACT Dx Factor V Leiden and Factor II Genotyping Test. A series dilution of input DNA levels ranging from 25 ng down to 0.0015 ng was used. The limit of detection was very similar for wild type, heterozygous and homozygous mutant alleles for both loci, and is 0.67 ng per reaction. The recommended input DNA level is 25 ng per reaction.

Carry-over Contamination

A study to evaluate cross contamination and carry-over was conducted with a panel of 3 clinical genomic DNA samples and a no template control sample. No cross contamination or carry-over was observed as all the no template control samples produced the expected no-call results after the runs.

Interferences

Leukocyte-depleted whole blood specimens spiked with cell lines from individuals encompassing all relevant genotypes for both the Factor V and Factor II genes were used in this evaluation. The following substances, at the concentrations listed below, were evaluated for their potential interfering effect on the test results.

- Hemoglobin, 200 mg/dL
- K2-EDTA, 3.4 µM
- Heparin, 3000 units/L
- Cholesterol, 500 mg/dL
- Bilirubin, 60 mg/dL
- Ethanol, 500 mg/dL

These substances are representative of metabolites produced during pathological conditions (endogenous) or compounds introduced during sample preparation (exogenous). All the substances were added to whole blood samples before genomic DNA extraction, except ethanol, which was added after the DNA extraction. None of the substances tested adversely impacted the performance of the IMPACT Dx test.

Reproducibility

The reproducibility of the IMPACT Dx Factor V Leiden and Factor II Genotyping Test was assessed at three external clinical sites. Twelve human genomic DNA samples, including all genotypes (wild type (GG), heterozygous mutant (GA) and homozygous mutant (AA) for both FV and FII genes) were used in this study. Each DNA sample was tested in singlet by each of 3 sites using one discrete IMPACT Dx System at each site. Two operators each conducted 5 runs on 5 non-consecutive days for a total of 10 testing runs per site. The number of correct calls, defined as the number of samples yielding the expected genotypes for both FV and FII genes, no calls and mis-calls were calculated for each operator, and all sites and operators combined. All operators, except one, from all 3 sites produced 100% agreement between the genotypes after all no call results were retested. One operator (Operator 2, Site 1) had 2 samples yielding repeated no calls; there were no mis-calls.

H. Clinical Data

In a method comparison study, 860 clinical samples were tested in the IMPACT Dx Factor V Leiden and Factor II Genotyping Test and compared to bi-directional sequencing reference method. Table H.1 presents the percent agreement between the IMPACT Dx Factor V Leiden and Factor II Genotyping Test and the reference method along with the respective lower confidence boundary (LCB) of the 95% confidence interval (CI) for Factor II. Table H.2 presents similar information for Factor V.

The test demonstrated an overall percentage agreement of 99.4% (CI: 98.6 – 99.8%) and 99.3% (CI: 98.5 – 99.7%) for the Factor II and Factor V genes, respectively, with the reference method.

Table H.1

Comparison of the IMPACT Dx Factor V Leiden and Factor II Genotyping Test and DNA Sequencing Results – Factor II

Genotype By Sequencing	# Samples	Number of FII Calls Before Repeat Testing					Number of FII Calls After Repeat Testing					
		Correct Calls	# No Calls[1]	# Missed Calls[2]	% Agreement	95% LCB[3]	Correct Calls	# No Calls[1]	# Missed Calls[2]	# Repeat Samples[4]	% Agreement	95% LCB[3]
Wild Type	762	747	15	0	98.0	97.0	757	5	0	15	99.3	98.5
Heterozygous	78	77	1	0	98.7	94.1	78	0	0	1	100.0	97.1
Homozygous	19	19	0	0	100.0	88.6	19	0	0	0	100.0	88.6
All Samples	859	843	16	0	98.1	97.0	854	5	0	16	99.4	98.6

Table H.2
Comparison of the IMPACT Dx Factor V Leiden and Factor II Genotyping Test and DNA Sequencing Results – Factor V

Genotype By Sequencing	# Samples	Number of FVL Calls Before Repeat Testing					Number of FVL Calls After Repeat Testing					
		Correct Calls	# No Calls[1]	# Missed Calls[2]	% Agreement	95% LCB[3]	Correct Calls	# No Calls[1]	# Missed Calls[2]	# Repeat Samples[4]	% Agreement	95% LCB[3]
Wild Type	710	697	13	0	98.2	97.1	706	4	0	13	99.4	98.6
Heterozygous	132	127	5	0	96.2	92.2	130	2	0	5	98.5	95.3
Homozygous	18	18	0	0	100.0	88.0	18	0	0	0	100.0	88.0
All Samples	860	842	18	0	97.9	96.7	854	6	0	18	99.3	98.5

When the heterozygous and homozygous mutant genotypes are combined into one "Positive".category and compared to one "Negative" (wild type) category, the test demonstrated a positive percent agreement or clinical sensitivity of 100.0% (95% CI: 96.3 – 100.0%) and a negative percent agreement or clinical specificity of 99.3% (95% CI: 98.5 – 99.8%) for Factor II. Similarly, for Factor V, positive percent agreement or clinical sensitivity was 98.7% (95% CI: 95.3 – 99.8%), and negative percent agreement or clinical specificity was 99.4% (95% CI: 98.6 – 99.8%) for Factor V.

I. Conclusion

The intended use of the IMPACT Dx Factor V Leiden and Factor II Genotyping Test is to measure a single point mutation (G1691A, referred to as the Factor V Leiden mutation or FVL) of the Factor V gene, located on Chromosome 1q23, and a single point mutation (G20210A) of the prothrombin gene (referred to as Factor II or FII), located on Chromosome 11p11-q12, from genomic DNA isolated from EDTA anti-coagulated human whole blood samples as an aid in the diagnosis of patients with suspected thrombophilia.

Performance data demonstrate that the IMPACT Dx Factor V Leiden and Factor II Genotyping Test using the IMPACT Dx System is as safe and effective as predicate devices. Thus the IMPACT Dx System and the IMPACT Dx Factor V Leiden and Factor II Genotyping Test are substantially equivalent to the other legally marketed devices, supporting premarket 510(k) clearance.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

June 13, 2014

Sequenom, Inc.
Ms. Robin Weiner
Senior Vice President, Quality and Regulatory Affairs
3595 John Hopkins Court
San Diego, CA 92121

Re: K132978
Trade/Device Name: IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test on the IMPACT Dx™ System
Regulation Number: 21 CFR 864.7280
Regulation Name: Factor V Leiden DNA Mutation Detection Systems
Regulatory Class: Class II
Product Code: PHJ
Dated: May 13, 2014
Received: May 14, 2014

Dear Ms. Weiner:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803); good manufacturing practice requirements as set

forth in the quality systems (QS) regulation (21 CFR Part 820); and if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to http://www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm for the CDRH's Office of Surveillance and Biometrics/Division of Postmarket Surveillance.

You may obtain other general information on your responsibilities under the Act from the Division of Industry and Consumer Education at its toll-free number (800) 638-2041 or (301) 796-7100 or at its Internet address http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/default.htm.

Sincerely yours,

Reena Philip -S

Reena Philip, Ph.D.
Director
Division of Molecular Genetics and Pathology
Office of In Vitro Diagnostics and Radiological Health
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: January 31, 2017
See PRA Statement below.

510(k) Number *(if known)*
K132978

Device Name
IMPACT Dx™ Factor V Leiden and Factor II Genotyping Test on the IMPACT™ Dx System

Indications for Use *(Describe)*
The IMPACT Dx Factor V Leiden and Factor II Genotyping Test is a qualitative in vitro diagnostic device intended for use in the detection and genotyping of a single point mutation (G1691A, referred to as the Factor V Leiden mutation or FVL) of the Factor V gene, located on Chromosome 1q23, and a single point mutation (G20210A) of the prothrombin gene (referred to as Factor II or FII), located on Chromosome 11p11-q12, from genomic DNA isolated from EDTA anti-coagulated human whole blood samples. The test is to be performed on the IMPACT Dx System and is indicated for use as an aid in the diagnosis of patients with suspected thrombophilia.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

PLEASE DO NOT WRITE BELOW THIS LINE – CONTINUE ON A SEPARATE PAGE IF NEEDED.

FOR FDA USE ONLY

Concurrence of Center for Devices and Radiological Health (CDRH) *(Signature)*

Donna M. Roscoe -S

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